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(ALVEOLAR GLIOMA?)

CONTAINING TUBERCLES AND TUBERCLE BACILLI.

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BY

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ON A POLYMORPHOUS CEREBRAL TUMOR

(ALVEOLAR GLIOMA?) CONTAINING TUBERCLES AND TUBERCLE BACILLI.*

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The classification of tumors of the brain and its membranes has been considerably modified since the early days when all such neoplasms were referred to one of the two main tumor groups—to the so-called fibrino-plastic or to the cancerous growths. By improved methods of microscopic technique investigators have still further added to our knowledge of the histological structure and the histogenesis of tumors, so that now, in the light of modern research, the classification of brain tumors must be still further remodeled, and the grouping under each class to a certain extent recast.

In the earliest times all tumors were classified according to their clinical symptoms, and types were recognized mainly as benign and malignant. Later their morphological characteristics were made the criteria for diagnosis. Tumors are now named also according to their histogenesis.

* Read before the twenty-third annual meeting of the Alumnæ Association of the Woman's Medical College of Pennsylvania, held May 19 and 20, 1898.

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663

With both histogenesis and morphology ascertained, a mistake in diagnosis is scarcely possible, though additional factors are of value in determining the nature of the growth.

Such definite rules for guidance in the diagnosis of tumors would seem to make a definite classification quite possible. But, as will be seen later, the origin of many tumors is difficult to trace, and the morphology is not always typical in itself of the normal type of tissue from which the tumor springs.

In a general way, then, it may be said that a positive diagnosis can be made only:

1. From histogenesis—(*a*) where the initial stage of the developing tumor can be certainly traced, or (*b*) where the periphery of an older growth shows the transition from normal to atypical structure.

2. From morphology—where the tumor occurs in an organ not normally possessing elements which could give rise to neoplasms of structure similar to each other if, at the same time, it can be shown whether or not the origin was from embryonic misplacement or from metastatic germs.

In other cases an approximate diagnosis may be formed, but a decisive conclusion can not be reached.

It will thus be seen that any classification of brain tumors which can be made must of necessity be more or less faulty, and that a certain number of tumors will always be referred to classes to which they do not properly belong.

The classification of brain tumors, as given in the various text-books on pathology, is more or less uniform. Such tumors are classified according to their points of origin—(1) from the *brain substance*, and (2) from *the meninges, the chorioid plexuses, and the ependymal lining of the ventricles.*

The *tumors of the brain substance* are glioma, together with neuro-glioma; sarcoma, including endothelioma, psammoma, glio-sarcoma (?), and various other mixed forms; cholesteatoma, angeioma, fibroma, osteoma, lipoma, dermoid cyst, epithelial growths which

may have penetrated the cerebral substance from the chorioid plexus or the ependymal lining of the ventricles; and secondary growths, such as sarcoma and carcinoma.

The *tumors of the meninges, the chorioid plexuses, and the ependymal lining of the ventricles* include the various forms of sarcoma, of which the endothelioma (alveolar sarcoma) is by far the most frequent variety; psammoma, cholesteatoma, fibroma, lipoma, chondroma, osteoma, carcinoma (?), ecchondroma, dermoid cysts, and secondary tumors (carcinoma and sarcoma).

Of these neoplasms the glioma group is peculiar to the central nervous system, arising, as it does, from histological elements found normally in the central nervous system only. It, together with the sarcoma group, forms the most common variety of tumor found in the brain.

The other types of cerebral neoplasm are rare. This is especially true of the epithelial group. But while this fact is founded upon experience, it would seem *a priori* most plausible to believe that neoplasms may often arise from the epithelial lining of the chorioid plexuses and of the ventricles, as do similar growths from the other epithelia of the body. The literature, however, has shown this not to be the case, since most of the cerebral neoplasms described as carcinoma and epithelioma are shown, both from description and illustration, to belong to the endothelial group. The cases of Eberth * and Arndt † are certainly examples of this latter type of growth. Rokitansky's ‡ case of "carcinoma" is based on insufficient evidence; Walther Selke's # description was of a papilloma in which he believed it possible for carcinoma to develop; while the

* Eberth. Zur Entwickelung des Epithelioms (Cholesteatoms) der Pia und der Lunge. Virchow's *Archiv*, xlix, 1870, 51.

† Arndt. Ein Cancroid der Pia mater. Virchow's *Archiv*, li, 1870, 495.

‡ Rokitansky. *Lehrbuch der path. Anat.*, ii, 1856, 426.

Selke, Walther. Ueber ein epitheliales Papillom des Gehirns. *Dissertatio inaug.*, Königsburg, 1891.

only authentic cases of primary epithelial tumor of the brain which I have found in the literature are those of Ziegler,* who reported a case of "carcinoma" originating in the chorioid plexus of the third ventricle; of Cornil and Ranvier,† who reported a case of "carcinoma" of the third ventricle which had originated from the ependyma; and a case of von Wunschheim,‡ in which a primary "carcinoma" of the fourth ventricle was shown to have its origin at the point of transition between the ependymal epithelium and the plexus epithelium.

In view of the general frequency with which glioma and endothelioma occur, and of their possible bearing upon the tumor to be described, the leading characteristics of these two groups may be considered in some detail.

The glioma is by far the most common type of tumor found in the brain, developing, as it does, from the neuroglia. Since the recent researches of Golgi and von Kölliker, and the still later investigations of His, Ramón y Cajal, von Lenhossék, and others, upon the embryology and histology of the normal brain, pathologists have also gained a more intelligible appreciation of abnormal processes. And now, by basing the diagnosis of glioma upon histogenetic as well as upon structural peculiarities, a more ready differentiation of the tumor groups is rendered possible.

It is thus that Stroebe # and other pathologists have applied these facts in their investigations upon glioma and have given a more comprehensive view of the entire subject. By the use of Weigert's and Mallory's differential stains and other improved methods of technique they have added to our knowledge of both the

* Ziegler. *Lehrbuch der path. Anat.*, 6. Aufl., spec. Theil, p. 370.

† Cornil and Ranvier. *Manuel d'histologie pathologique*, i, 1881, 703.

‡ Von Wunschheim. Ueber ein Fall primärem Carcinom in der Rautengrube. *Prag. med. Woch.*, xvi, 1891, 337.

Stroebe. Ueber Entstehung und Bau der Gehirngliome. Ziegler's *Beiträge*, xviii, 1895, 405.

morphology and the histogenesis of glioma. They have shown, at the same time, that many tumors heretofore described as sarcoma, glio-sarcoma, neuro-glioma, etc., are to be included under the simple glioma species.

Stroebe, in his comprehensive monograph, *Ueber Entstehung und Bau der Gehirngliome*, has given a thorough survey of the literature upon glioma from the initial publication of Virchow * up to the time of his own investigation. He has communicated the results of six carefully studied cases of his own, and gives some interesting conclusions. Before going into the details of Stroebe's work upon pathological neuroglia it will be well to consider briefly the prevailing conceptions of normal neuroglia as this tissue is now understood.

The neuroglia is functionally and anatomically the connective tissue of the central nervous system. It was formerly thought to be a mesodermal structure like the other connective tissues of the body, but more recent investigations have shown it to be derived from the ectoderm. In structure it consists of fibres and cells, the fibres being woven into a delicate glistening network, while the cells are small, apparently branched, and are intimately intermingled with the network of fibres. The progenitors of the neuroglia cells are the embryonic ependymal cells, and probably certain less differentiated elements known as astroblasts. The normal neuroglia thus presents, in the course of its development, mainly three different types of cells—cells of ependymal type; cells of a simple and undifferentiated form, or astroblasts; and the spider and brush cells, or astrocytes.

With regard to the relation of the neuroglia fibre to the neuroglia cell there exists considerable difference of opinion. It was formerly thought that the fibre was a direct protoplasmic outgrowth from the cell body, and Golgi's silver method did much to further this belief. It has since been claimed by Weigert that this relation of fibre to cell holds good only for embryonic

* Virchow. *Die krankhaften Geschwülste*, Berlin, 1863.

forms, while a separation exists in adult cells. This position is made probable by the use of his differential chemical stain, and has been further confirmed by the researches of Mallory and others.

Stroebe, on the other hand, believes that there is insufficient evidence for the acceptance of Weigert's claim, and still adheres to the view of direct continuity of structure for both adult and embryonic forms. And Taylor,* although admitting the "essential correctness" of Weigert's view, takes a position between the two extremes and suggests the existence, even in developed neuroglia, of a certain number of neuroglia elements whose fibres are still in the relation of physical continuity with the cells. His careful researches have led him to conceive of the "evolution of neuroglia from cells without processes to cells with processes, and then to cells whose processes have been completely differentiated into fibres." It is probable that this more conservative position is correct, but that, as Taylor further states, "with all the means at our command the absolute determination of the relation of cells and fibres in individual cases remains difficult and at times impossible."

Stroebe has shown that gliomata of the central nervous system arise from a tissue whose elements take their origin from the neuroglia or from the ependymal cells. In support of this view he cites numerous cases of glioma from the literature; but especially confirmatory is a case of his own in which cavities lined by ciliated cylindrical epithelium were found in the middle of a glioma. In this latter case the pointed extremities of the epithelial-like cells which lined the cavities were drawn out into fine filamentous processes which were intimately interwoven with the surrounding network of neuroglia fibres—all properties analogous to those which belong to the ependymal cells of the ventricles and the neural canal. And because of this analogy Stroebe regards the cavities as abnormal lateral offshoots

* Taylor. A Contribution to the Study of Human Neuroglia. *Journal of Experimental Medicine*, vol. ii, 1897, p. 611.

from the primitive neural canal, which originated in a disturbance of development occurring in the early embryo. That the cavities were no longer in connection with the ventricle he regards as insignificant, in view of the fact that the offshoots must have become more and more deeply situated as development went on, until they were finally shut off from all communication with the primitive canal.

At the time of Stroebe's publication there was but one other case on record in which a cerebral glioma contained cystlike formations with an incomplete lining of cubical epithelial-like cells. This was a case reported by Buchholz,* and resembled Stroebe's case in all essentials except that here the "epithelium" possessed no cilia.

Since the reports of Buchholz and Stroebe there has appeared in the literature, so far as I can find, but one similar case. This was recently reported by Henneberg,† and concerned a cerebral glioma which contained cavities lined with cylindrical "epithelium." Here, as in the case of Buchholz, the cells possessed no cilia.‡

Curiously enough, these three cases, with almost identical anatomical features and representing the entire literature upon this class of cerebral tumors, have been differently interpreted by each of the three observers. Stroebe, as said, regards his case as the result of embryonic misplacement from the primitive neural canal. Buchholz interprets the "epithelium" in his case as transformed glioma cells which, as the derivatives of glia cells, have an ectodermal origin. These

* Buchholz. Beitrag zur Kenntniss der Gehirngliome. *Archiv für Psych.*, xxii, 1891.

† Henneberg. Beitrag zur Kenntniss der Gliome. *Archiv für Psychiat. und Nervenkrankh.*, xxx, 1898, 205.

‡ Since the completion of this paper Rosenthal (Ueber eine eigent thümliche, mit Syringomyelie complicirte Geschwulst des Rückenmarks. Ziegler's *Beiträge*, xxiii, 1898, 111) has alluded to a tumor of the fourth ventricle, of which he has seen a section, the description of which is to be published by Glücksmann. This will make the fourth case of such tumor reported.

glioma cells, he thinks, under certain conditions, such as pressure, may take on an epithelial-like form. Henneberg attributes the epithelial-lined cavities in his case to the outgrowth of gliomatous excrescences into the lateral ventricle, which, as they progressed outward, had left portions of the ependyma deeply sunk in the tumor. These portions subsequently developed into the cavities described. It is probable that all three cases are representative of the same general pathological condition, and that the theory of embryonic misplacement, advanced by Stroebe and bearing out the Cohnheim hypothesis, may be taken to explain them all.

In further support of this theory of histogenesis are numerous other pathological processes of both brain and cord in which epithelial-lined cavities exist, often still maintaining their connection with the ventricle or the central canal. The cavities in these various processes are not always interpreted as the result of embryonic misplacement by the observers who reported them, but they seem to us conclusive of this view. Such are the many cases of syringomyelia containing epithelial-lined cysts, and the isolated cases of multiple sclerosis (Borst), teratoid tumor (Saxer), hydrocephalus (Henneberg). granular ependymitis (Aschoff), and other cases in which epithelial-lined cavities are found. The literature on this subject has been carefully collected by Stroebe,* and has been still further augmented by Henneberg.†

The structural peculiarities of glioma vary within very wide limits, including all types of neuroglia tissue, both normal and pathological, and all stages of neuroglia formation from the earliest embryonic to the developed adult forms. But while this variation is in itself a peculiarity of the tumor-forming process, there are yet certain leading characteristics by which the glioma may be known. These characteristics include in a general way (*a*) the presence of stellate neuroglia cells and (*b*) a fine meshwork of highly refractile fibres

* Stroebe. *Op. cit.*

† Henneberg. *Op. cit.*

which show in most cases a direct connection with the cells. The cells vary in size and shape. Some of them possess numerous fine, short, filamentous processes. Others have coarse, long fibres that are branched. The fibres may be fine or coarse, and the meshwork which they form is loose or dense.

The gliomata are named for the most part according to the element which predominates. Thus, there are fibrous gliomata and cellular gliomata; there are coarse-fibred tumors and fine-fibred forms. There are types of gliomata according to the variety of cell, from the earliest embryonic form to the large ganglion cell-like (neurogliomatous?) element, and there are types in which all transitional forms are found.

According to this nomenclature one finds gliomata classified as fibrous and cellular (Raymond); as spider-celled glioma and brush-celled glioma (Simon); and by Stroebe as small-celled glioma, large-celled glioma, and giant-celled glioma; as cellular (soft) glioma and fibrous (hard) glioma; as star-celled glioma, spindle-celled glioma, polymorphous-celled glioma, and ganglion-celled glioma; as coarse-fibred glioma and fine-fibred glioma; as dense glioma (hard) and loose glioma (soft); and (according to location) as central glioma, peripheral or superficial glioma, and intermediate glioma.

The most recent contribution to the classification of gliomata has been made by Dr. Flexner.* In a paper upon Glia and Gliomatosis, read before the Philadelphia Neurological Society, February 28, 1898, he reported a tumor, heretofore undescribed in the literature, to which he gives the name ependyma-celled glioma. It was composed of cells which resembled the ependymal type of cell found in the human embryonic spinal cord.

Dr. Flexner classifies gliomata according to their correspondence with certain forms or stages of development of neuroglia, and thus recognizes: (1) tumors made up of cells of simple form corresponding with the

* Flexner. Glia and Gliomatosis. *The Journal of Nervous and Mental Disease*, vol. xxv, 1898, p. 306.

astroblast; (2) tumors which contain cells of more complex type corresponding with Deiters's cell, or the astrocyte; and (3) tumors composed of cells resembling the early embryonic ependymal forms.

He further adds that although such a tumor has not yet certainly come to his notice, "it is conceivable that the fully developed or adult ependymal cells may also give rise to tumors whose appearance would be different from the several forms already described." *

The more or less precise description of the structure of glioma, even though broad in its scope, and the recognition of the genesis of glioma from the ectoderm have, as already said, been made the basis of differential diagnosis for the various tumors of the central nervous system.

Stroebe, in his scheme of differentiation between glioma and sarcoma, lays particular stress upon the close relation of the glia fibre to the glia cell, and upon the peculiar, highly refractile, fibrous network found between the cells. In sarcoma these features are wanting, though there may be occasional cells with processes. Stroebe further considers the mode of growth, and finds that glioma invades the brain as a diffuse infiltration, while sarcoma is usually more or less circumscribed, compressing the brain substance, which, however, it does not infiltrate. In glioma the pial membranes are often intact, or are at most but slightly thickened; in sarcoma they are adherent, forming an integral part of the tumor mass. Medullated nerve fibres are found almost invariably in glioma; in sarcoma, when present at all, they are situated in the periphery. Sarcoma is often associated with mucoid degeneration; glioma

* Rosenthal, in the paper previously alluded to, has described a tumor under the name of neuroepithelioma gliomatosum microcysticum, which shows, among other appearances, typical adult ciliated ependymal cells with processes. This tumor is regarded by the author as having originated from the same embryonic structures that give rise to the central nervous system, but under somewhat different conditions, leading to the formation of an adenomalike tumor structure. He finds in support of this view not only adult ependymal cells, but also these same elements in other stages of development.

shows at most an œdematous softening. Where the origin can be traced to the glia on the one hand, or to the connective tissue about the blood-vessels or the membranes on the other, there will, of course, be no difficulty in diagnosis.

While this scheme for differentiation is not generally accepted, it is applicable to a large number of cases.

The diagnosis is difficult for those gliomata alone in which the component cells are mainly astroblasts, since these undifferentiated cells have many features in common with the undeveloped cells of the mesoblastic connective tissue. Indeed, it is impossible at times to distinguish between the astroblastic glioma and the small round-celled sarcoma, and such tumors have often given rise to the anomalous term glio-sarcoma.

The question of the existence of a mixed tumor of the nature of glio-sarcoma has been sufficiently discussed in the recent literature, and thus demands but a word of mention. Such a nomenclature is conceded by most of the leading pathologists to be scientifically incorrect as applied to a simple form, since the term as now applied would refer to tumors of mixed epiblastic and mesoblastic origin—that is, to those whose structures are derived in part from neuroglia and in part from the connective tissue of the blood-vessels or meninges of the brain. There is, moreover, according to von Lenhossék, no authentic case of glio-sarcoma on record.

It is easy to conceive of this misuse of the term in the early days when Virchow first defined glioma. The glia tumors were then believed to be derived from the mesoderm in the same manner as the simple connective-tissue tumors, and morphological features were made the basis of differentiation. At that time there was no sharp border line between glioma and sarcoma. A very cellular glioma was believed to be a transition stage to the medullary sarcoma, and the choice of a name was voluntary. Now that histogenesis is the primary determining factor in diagnosis, it is surprising

that such men as Hansemann,* Henneberg,† and Thoma still adhere to the old method of nomenclature.

It has been seen, however, that these difficulties of nomenclature hold good nowadays for only a limited number of cases. Even where the histogenesis can not be traced it is possible by the application of many different stains to bring out the structural peculiarities of the tumor. The very cellular glioma recently described by Taylor,‡ Henneberg's # cases of glioma with sarcomatous degeneration, and possibly the peculiar cellular tumor described by Alice Hamilton || as "neuro-glioma," would all in former times have been referred to the sarcoma group. And, conversely, it may be said that the recent schemes for the separation of glioma and sarcoma, founded as they are upon both histogenetic and structural differences, would refer most of the so-called sarcomata, glio-sarcomata, and neuro-gliomata heretofore described to the simple glioma group. This is true of almost all very cellular tumors, which are still interpreted as sarcomata when inadequately studied by the older methods alone.

The endothelioma is the form of tumor most often met with in the internal meninges, and next to glioma is the most frequent variety of neoplasm found in the brain. It may be defined as a tumor of alveolar or tubular structure, which takes its origin from the endothelial cells. The alveolar and the tubular structure may be lost in places through a diffuse proliferation of the growth.

This definition of endothelioma would be very simple if there were complete concurrence of opinion as to what constitutes endothelial cells, if the histogenesis of the tumor could be certainly traced from the endo-

* Hansemann. Ueber die Histogenese der bösartigen Geschwülste. *Die mikrosk. Diagnose der bösartigen Geschwülste*, Berlin, 1897, p. 165.

† Henneberg. *Op. cit.* ‡ Taylor. *Op. cit.*

Henneberg. *Op. cit.*

|| Thomas, H M., and Hamilton, Alice. The Clinical Course and Pathological Histology of a Case of Neuro-Glioma of the Brain. *The Journal of Experimental Medicine*, vol. ii, 1897, p. 635.

thelial cells, and if the structure of the tumor were uniformly tubular or alveolar. But each of these questions has given rise to much discussion. Indeed, the term endothelioma has been the subject of numerous controversies from its first introduction by Golgi down to the present time. Various views as to its significance are still held by competent observers, some even denying the existence of such a growth. Without entering into these discussions it is worth while only to refer to the early work of Golgi, Waldeyer, and Kolaczek, and the more recent work done by Hansemann,* Ribbert,† von Volkmann,‡ Lubarsch,# and others who have done much to collect the scattered literature. A brief outline of the more tenable theories may be given. Ziegler,‖ in the last edition of his text-book on pathology, defines endothelioma as an organoid sarcoma in which groups and strands of cells result from the proliferation of the endothelium lining the lymph spaces and the lymph vessels. In other words, the endothelioma is a lymphangeiosarcoma of alveolar or tubular structure. This definition will be seen to differ somewhat from that expressed in the previous editions of Ziegler's work, excluding as it does from the endothelioma group all new growths which arise from the perithelium covering the blood-vessels, and even such tumors as develop from the endothelium lining the blood-vessels and serous cavities themselves. It thus limits the class of endothelioma to a decidedly smaller group.

A broader definition is that of von Volkmann, who includes among the endotheliomata all neoplasms which arise from the developed endothelial cells, whether these line the blood-vessels, the lymph vessels, the

* Hansemann. *Op. cit.*

† Ribbert. Ueber das Endothel in der pathologischen Histologie. *Vierteljahresschr. d. naturf. Gesellsch. in Zürich*, Jahrg. 41.

‡ Von Volkmann. Ueber endotheliale Geschwülste, etc. *Deutsche Zeitschrift für Chirurgie*, xli.

Lubarsch. Hyperplasie und Geschwülste. *Ergebnisse der allg. Path.*, ii, 1895, 366; and Endotheliom. *Ergebnisse der allg. Path. und path. Anatomie*, Wiesbaden, 1897.

‖ Ziegler. *Allg. path. Anat.*, 9. Aufl., 1898, 430.

lymph spaces, the serous cavities, or whether they form a flat perivascular covering for the blood-vessels. In the brain it will thus be seen that the endothelioma develops from the endothelium covering the delicate connective tissue trabeculæ of the membranes, or it may arise from the perithelium of the cortical blood-vessels.

Where the histogenesis can be traced to the endothelium, as it usually can in the brain, there should be no doubt as to the nature of the growth. Von Jannsen's * case is a typical example of endothelioma traceable to the cerebral membranes, while Carter's † cylindroma may be referred to the blood-vessel sheaths. Where the histogenesis can not be traced to the endothelium the morphology is more or less conclusive, especially in those cases where the type of blood-vessel or lymph vessel with its corpuscular elements is retained. The difficulty still remains where the endothelioma resembles carcinoma, adenoma, simple sarcoma, or, indeed, a combination of the three. The alveoli in such cases may be lined with flat, cuboidal, or cylindrical epithelial-like cells, and may present a variety of degenerations of stroma, of cells, or of both.

Von Volkmann's definition has the advantage of establishing a nomenclature based upon histogenesis alone; and this histogenesis, as clearly indicated, is directly from endothelial cells. It would thus remove from the literature the more or less ambiguous terms which refer to structural peculiarities, and which include both epithelial and endothelial tumors among the present group.‡ Such ambiguous terms are those proposed by Bizzozero, Orth, Klebs, Hansemann, Lubarsch, and others, and include the names angeiosarcoma, perithelioma, hæmangeiosarcoma, lymphangeiosarcoma, an-

* Von Jannsen. Ein Sarcom der Pia mater. Virchow's *Archiv* cxxxix, 1895, 213.

† Carter. A Case of Cylindroma of the Brain. *Journal of Pathology and Bacteriology*, vol. i, 1893, p. 384.

‡ Such cases have been brought forward by Ammann and Köster, the former of whom allows either an endothelial or an epithelial origin for endothelioma, while the latter admits equally an origin from endothelium or epithelium for epithelial tumors.

geiosarcoma endothelioides, cylindroma, endotheliofibroma, and endothelial carcinoma.

For the practical separation of endothelioma and carcinoma von Volkmann's definition is not sufficient, in that endothelium is often not to be distinguished morphologically from epithelium; and the actual origin of the tumor may often be determined only by exclusion. Indeed, Ribbert has shown that the histogenesis of a tumor, even in its peripheral parts, is often not to be recognized with certainty, since endothelioma and epithelioma may give rise to similar microscopic pictures. And what von Volkmann interprets as the transition from the endothelioma cell to the normal flat endothelium of the lymph spaces, Ribbert equally regards as carcinoma penetrating the neighboring tissues in the form of thin, flat epithelial cells.

It is scarcely possible to find sharp differential lines between these two forms of tumor. But Lubarsch * believes that more may be gained from a careful study of the finer histological structure of the cells than from the histogenesis. Such structural differences he finds in the coarser granulation of the protoplasm in the cells of epithelial tumors, in their irregular mitoses (Hansemann), in the occasional demonstration of prickles, and in the formation of keratohyalin—features absent from cells of endothelial origin.

What Lubarsch has said of endothelial tumors may be said of tumors in general: "It is wrong to apply only one criterion or but one method of examination in determining the nature of the growth. The more exact the histological examination and the more careful the study of the morphological relations and of the gross anatomical structure, the smaller will be the number of doubtful cases. But even then there must always remain a number of cases as to the nature of which the first authorities can not agree."

The case about to be reported occurred in the service of Dr. Cohen, of Bay View Asylum, and was brought

* Lubarsch. *Op. cit.*

to the pathological laboratory of the Johns Hopkins University by Dr. Henry J. Berkley, to whom I am indebted for the brief clinical notes and the autopsy record.

Clinical History.—X. Y., aged approximately sixty-five years, was admitted to the W. F. H., Bay View, November, 1897, and died three days after. When admitted the woman had full consciousness, but was totally unable to enunciate, nor was there any history that accompanied her. She gradually became comatose, and died in the coma.

Autopsy Record.—The autopsy was negative, except as regards the brain. In the left temporo-sphenoidal lobe was found a tumor, deeply situated (Fig. 1). It was about three by four centimetres in size, and had an area of necrotic tissue surrounding it about half a centimetre in width. The tumor occupied about two thirds of the left temporo-sphenoidal lobe, corresponding with the second, the lower portion of the first, and the upper portion of the third temporal convolutions. It extended inward, pressing upon the convolutions of the island of Reil. Only at one point did the mass approach the surface. The necrotic area was more noticeable toward the upper portion of the lobe than in the inferior regions. There were no metastases found in the brain or other organs, nor was there any evidence of tuberculosis.

Naked-eye Appearance of Alcohol-hardened Specimen.—The tumor is an irregularly lobulated mass with smooth surface, and covered by a membranelike tissue, from which project numerous filamentous processes. Its color is grayish white, its consistence is firm and elastic. On section through the mass the cut surface presents an opaque yellowish-white color, dotted and streaked with fine lines of translucent gray (Fig. 2). This gray substance finds a marked development in the centre, where it forms a trabeculated network. Within the gray substance are several small circumscribed areas of necrosis (Fig. 2, N). At one point the tissue is soft and spongelike, despite alcohol hardening. From this spongelike tissue the capsule can be removed with moderate ease, but at other points it is firmly adherent.

Histological Examination.—Serial sections were made, and many slides were stained by the following method: 1. Hæmatoxylin and eosin. 2. Mallory's phosphotungstic-acid-hæmatoxylin. 3. Mallory's phospho-

molybdic-acid-hæmatoxylin. 4. Van Gieson's picric-acid-fuchsine. 5. Weigert's fibrin stain. 6. Gabbet's carbol-fuchsine. Unstained specimens were also examined in glycerin. The sections stained with hæmatoxylin and eosin are most satisfactory as presenting the greatest variety of lesions. The following description, however, is the result of the examination of many sections stained by the different methods.

With low magnification there is found a capsule extending completely around the tumor, dipping down between its convolutions, and sending processes into the mass, whose structure is thus broken up into more or less imperfect lobules. The capsule is loosely connected with the tumor in some places, quite separated at others, but for the most part intimately adherent. In some places it is more or less homogeneous, again it is distinctly fibrillated and cellular. Here it is broad, there it tapers off to a narrow band. And at all points except in the homogeneous areas it gives the appearance of lamellation.

Of the tumor proper the lobules are most distinct near the periphery but fuse toward the centre, where they lose themselves in a loose-meshed reticulum or in necrotic foci.

The tumor shows a very varied structure in its different parts. Where the lobules are most circumscribed the type of growth is more or less uniform. Where they are less circumscribed transitions may be seen from one type of growth to another. Where the lobular character is lost these transitions are most marked.

Of the lobules, the structure in some places resembles that of simple medullary carcinoma (Fig. 3). It is made up of alveoli containing many hundred cells and surrounded by a very cellular stroma, which is continuous with the processes extending in from the capsule. The alveolar structure is made conspicuous because of the difference in the character of cells in alveoli and stroma. In some places this structure is emphasized by a distinct peripheral border of high cylindrical cells.

In other lobules the type of growth is that of tubular carcinoma or of adenoma (Fig. 4, *a*). The tubules sometimes contain a lumen, at others not. Sometimes they are lined by high cylindrical cells, at other times by low cuboidal or polyedral forms.

One nodule imbedded in the tumor is made up of a sarcomalike tissue containing giant cells (Fig. 5, *a*). It is diffusely cellular in the centre, but this diffuse cel-

lular growth can be traced as a transition from alveoli in the periphery of the nodule.

This nodule is partly surrounded by a wedge of tissue, made up of large branching alveoli which are lined by close-set cylindrical cells and are distinctly marked out by a fibrillated stroma (Fig. 5, *b*).

Toward the centre of the specimen, where the lobular arrangement is lost, are numerous blood-vessels, each surrounded by a distinct collar of cells which extend inward as far as to the intact intima (Fig. 6). These stand out conspicuously against a loose-meshed reticulum and give the impression of perithelial angeiosarcoma or endothelioma. There are also vessels not so surrounded, and the cell groupings may extend away from the vessels into the tissues, where they become continuous with the tubular alveoli above described or resolve themselves into a diffuse cellular tissue.

In other areas there is a diffuse arrangement of small polyedral cells mingled with highly refractile fibres. The high refraction is especially noted in the unstained sections mounted in glycerin, and is sometimes seen in those sections stained with hæmatoxylin and eosin. This appearance is suggestive of neuroglia fibres, and gives the impression of glioma formation. But at no time are the fibres found to be continuous with the cells, nor, indeed, do typical neuroglia cells occur.

Thus, of the many histological types of which this tumor is composed each one may be traced as a transition from some other. There are focal areas of necrosis and other features which can be best studied with greater magnification.

Under the high power the capsule is found to be made up of fibrillated connective tissue arranged in parallel lamellæ, between which are layers of small round cells. These cells extend into the tumor along the fibrous processes that divide the mass into lobules. Thence they extend into the lobules along the stroma about the alveoli. They even invade the alveoli at times, producing a diffuse admixture with tumor cells (Figs. 3 and 4). Accompanying the lymphoid cells are sometimes epithelioid cells, and an occasional giant cell with homogeneous protoplasm and peripheral arrangement of its nuclei.

These cells are sometimes grouped into discrete microscopic tubercles, which are mostly confined to the stroma, but at times involve the alveoli. When within an alveolus the tubercles often include the tumor cells

within their structure. By the use of Gabbet's carbol-fuchsine stain tubercle bacilli were demonstrated.

Infiltrating the tumor in places are also polymorphonuclear leucocytes. These are most numerous in the stroma. They accompany the small round cells in certain areas, and greatly predominate in others. Where they infiltrate the alveolus the alveolar structure is blurred. They are often associated with fibrin and necrosis. Pyogenic cocci could not be found (Weigert's fibrin stain). Within the blood-vessels are many polymorphonuclear leucocytes and thrombi. When the thrombi completely plug the lumen they are often surrounded by circumscribed areas of necrosis at times of considerable extent. These necrotic areas show either the faint outline of the original tumor structure or a granular texture with peripheral radiation of epithelioid cells.

That portion of the capsule which under the low power appeared homogeneous and highly refractile is found with greater magnification to be made up of a fine meshwork of fibrils, including small round cells. It resembles embryonic brain tissue where stained with hæmatoxylin and eosin, but is found to contain fibrin where Weigert's fibrin stain is used. The loose-meshed reticulum in the centre of the specimen is composed of œdematous fibrous (perhaps mucoid) tissue likewise infiltrated with fibrin and containing isolated tumor cells. The latter show different degrees of atrophy and various kinds of degeneration, for the most part fatty.

The individual tumor cells show many different forms. Where the structure conforms to the type of the simple medullary carcinoma the cells of the alveolus also conform to this type, being large, more or less uniform in size and shape, and containing much granular protoplasm and large round or oval vesicular nuclei. When the periphery of the alveolus is lined with cuboidal or cylindrical cells the nucleus of the cell lies deep down within the protoplasm at its basal attachment to the stroma.

Where the structure of the tumor resembles tubular carcinoma the cells are high cylindrical or low cuboidal. But when the tubules suffer from compression the lumen of the tubules is lost and the lining cells become small and polyedral or flat. The tubular texture thereafter passes over into mere lines of cells, which soon break up until all appearance of organoid structure is lost.

The nodule which contains a carcinomalike periphery and sarcomalike centre shows every transition

from the uniform alveolar structure of the one to the diffuse cellular texture of the other (Fig. 5, *a*). The cylindrical cells lining the alveolar wall give rise to numerous giant cells, which are at first continuous with the lining of the alveolus but are later pushed off into the interior, where they blend with other tumor cells. Finally, both cells and stroma lose their alveolar relation and appear more or less evenly distributed.

The giant cells of the tumor may be of any size and shape, but are usually many times larger than the average tumor cell. They contain one or several large nuclei or many small ones. The small nuclei are usually round and vesicular. The large nuclei are round, oval, or irregular in shape, and usually contain coarse chromatin granules which take a deep hæmatoxylin stain. Sometimes the nucleus is occupied by one or more hyaline-looking bodies, and the nucleolus itself may have undergone the hyaline change or may be distended with vacuoles or fat. Large budding nuclei and atypical nuclear figures, such as giant mitoses, multipolar mitoses, and forms showing karyorrhexis, are numerous. In the giant cells the nuclei are usually near the centre and are surrounded by a broad zone of granular protoplasm. But sometimes degeneration products distend the cell, push the nucleus to the periphery, and give the signet-ring effect.

The wedge of tumor tissue, made up of large branching alveoli, lies next to the last-mentioned nodule and contrasts sharply with it (Fig. 5, *b*). In the periphery of the alveolus the cells are uniformly high and cylindrical. In the interior they are small and polyedral.

In the centre of the tumor, where the structure resembles perithelial angeiosarcoma, the collars of cells surrounding the blood-vessels are made up for the most part of groups of tubules bound together by connective tissue, and lying parallel with the long axis of the vessel or oblique to it. Like the simple tubules described above, the individual tubules of these perivascular collars possess a lining of cylindrical, cuboidal, or polyedral cells. They also lose their tubular character in places and surround the vessels as a diffuse proliferative growth. Sometimes single rows of high cylindrical cells sit upon the vessel walls, with their free ends turned outward and the nuclei located in the basal portion of the cells. Occasionally a double row of such cells is seen, always with the nuclear end toward the vessel wall (Fig. 4, *b*).

The protoplasm of the tumor cells is usually coarsely granular, but various forms of degeneration may cause it to appear hyaline and homogeneous; fatty, pale, and trabeculated; vacuolated, or distended with single large droplets of fat. Besides these, cellular inclusions often exist.

Conclusions.—Thus it will be seen that the tumor under discussion presents the appearance of several histological types—carcinoma, sarcoma, and glioma. The carcinomalike areas are simple alveolar and tubular. The sarcomalike areas show the structure of simple sarcoma and of endothelioma. The areas which resemble glioma show a diffuse intermingling of tumor cells with highly refractile fibres. Moreover, transitions between the different histological types are found, showing that all must be regarded as different modifications of the same kind of growth.

If now we return for a moment to a consideration of the various forms of neoplasms which are known to develop from neuroglia we shall find that only those tumors have been regarded as carcinomata which have taken origin in the adult ependymal cell. If what has gone before is borne out, it is probable that the tumor under discussion is not a carcinoma in the true sense of the term, but only another form of glioma; and since its apparent tendency is to present itself in alveolar form, it might well be designated "alveolar glioma." This name has the twofold advantage of indicating the nature and origin of the neoplasm, and at the same time distinguishing it sharply from secondary, metastatic forms of cancer. According to this conception the tumor would correspond with such a one as was proposed by Dr. Flexner * to arise from the adult ependymal cells.

Applying the scheme for the diagnosis of tumors suggested at the beginning of this paper we find that in this case the initial stage of tumor formation can not be followed because the growth had progressed too far. The peripheral transition from atypical to normal tis-

* Flexner. *Op. cit.*

sue can not be traced because of encapsulation of the growth, and, unfortunately, the neighboring structures were not preserved. The tumor, furthermore, occurs in the brain, from which organ epithelium, in the ordinary sense, is normally absent; and it occurs in a part of the brain which has no connection with even the normal ependymal cells. This would not, however, exclude secondary growths, but such have already been excluded in this case by the findings at autopsy. The possibility of embryonic misplacement still remains.

There are few data, therefore, other than histological, upon which dependence can be placed in forming a definite diagnosis, and the latter are complex and confusing. Taking the histological type as the basis, together with what additional factors—clinical and other—may be found both for and against each growth, an attempt will be made at differentiation.

In favor of *carcinoma* are: (1) The alveolar and tubular structure of the tumor; (2) the epithelial-like type of cell, cylindrical, cuboidal, and polyedral; (3) the hyperchromatosis of the nuclei; and (4) the atypical nuclear figures (Hansemann).

Against carcinoma are: (1) The circumscribed character of the growth; (2) its apparent encapsulation; (3) certain diffuse sarcomalike areas found in portions of the tumor; and (4) the absence of tumor formation elsewhere in the body, which can be regarded either as primary or secondary to this growth.

Added to these may be mentioned (5) the infrequency with which carcinoma of the brain, either primary or secondary, has been found.

The complete separation of the tumor from the ventricles may be said to militate against the carcinoma theory, but not entirely to exclude it, since here, as in the epithelial inclusions described by Stroebe * and others, a separation of the tumor germs may have occurred in the early embryo.

In favor of *alveolar glioma,* as of carcinoma, are: (1) The presence of alveoli and tubules, and (2) the epi-

* Stroebe. *Op. cit.*

thelial-like character of the cells, which may be said to resemble chorioidal epithelium, as this is seen in preparations preserved in alcohol or allied fluids.

But an additional factor for alveolar glioma may be found in (3) the peculiar highly refractile neuroglialike fibrils scattered in places among the cells.

Opposing the theory of alveolar glioma are: (1) The absence of the typical ependymal cell characterized by its long filamentous process, and (2) the circumscribed character of the present growth, which is unlike the infiltrating nature of glioma. It is possible, however, that with more complex organization the glioma may take on new biological characteristics. (3) As a third opposing factor to alveolar glioma may be mentioned the complete separation of the tumor from the ventricle. But this, as in the case of carcinoma, would not exclude such gliomata as originate from embryonic inclusions.

In favor of *endothelioma* are: (1) The circumscribed character of the growth; (2) the absence of tumor formation in other organs of the body; (3) the arrangement about the blood-vessels in cellular cords which are themselves made up of groupings of tubules; and (4) the occasional transition from the more complex types to diffuse sarcomalike tissue. Indeed, this resolving of a complex structure into its simple constituents is more characteristic of endothelioma than of any other growth, and does much to render probable an ultimate diagnosis of endothelioma. And the arrangement in cellular cords about the blood-vessels is typically characteristic of that form of endothelioma known as perithelial angeiosarcoma.

(5) An additional point in favor of endothelioma is the fact that there are no positive data to oppose such a diagnosis. For every one of the types of tumor represented in this specimen may be interpreted as a different modification of the complex endothelial growth, while the less complex tumors—carcinoma and alveolar glioma—would be less apt to assume the perivascular form.

As to histogenesis, we have seen that in this

special case the initial stage of tumor formation can not be followed. Nor can a transition be shown in the periphery of the growth from atypical to normal tissue. But a consideration of the usual modes of genesis for the several types of neoplasm here represented may aid in the elucidation of this growth.

Carcinoma, as we have seen, is rare in the brain. Here, as elsewhere in the body, it is supposed to take origin from epithelial elements, whether adult or embryonic, and these elements are derived, as we know, from the ectoderm. The epithelia of the brain are the ependymal lining of the ventricles and the epithelium covering the chorioid plexuses. The so-called primary carcinoma of the brain would thus be found as a growth continuous with one or the other of these epithelial structures. Or, if due to an embryonic misplacement, the tumor might possibly be separated from the epithelium, lying deep within the medullary substance as a heteroplastic growth.

Glioma has been described as the most frequent variety of tumor found in the brain. Like carcinoma, it takes rise from cells originating in the ectodermal structures which for glioma are the several neuroglia elements.

It will thus be seen that the ependyma has been regarded as the starting point for two dissimilar neoplasms, the ordinary glioma and the carcinoma. It will therefore be of interest to inquire whether a distinction actually can be made between these two types of tumor.

That tumors having the morphological structure of carcinoma can originate in the ependyma is proved by the case of so-called "primary carcinoma of the fourth ventricle," reported by von Wunschheim, in which he has shown a direct connection between the ependymal epithelium and that covering the chorioid plexus on the one hand, and the epithelium of the tumor on the other. He believes that the place of transition between the ependymal epithelium and the plexus epithelium was the starting point of the tumor.

That glioma also springs from ependyma is shown by the presence of epithelial-lined cavities within certain gliomata, such as have been described by Stroebe, Buchholz, and Henneberg for the brain, and similar epithelial misplacements in the numerous cases of syringo-myelia with which the literature abounds.

That ordinary carcinoma and certain forms of glioma have hitherto been confounded is now clear.

Perhaps a solution to the difficulty may be found in the theory *that while both carcinoma and glioma are derived from the same blastodermic layer in the embryo, the ectoderm, they originate from this structure at different periods of its development.* The carcinoma may therefore correspond with the ectodermal cell of an earlier embryonic period, while glioma would be derived from the ectodermal cell after it has become differentiated into the spongioblast of the primitive neural canal.

According to this theory the term carcinoma may be applied only to those neoplasms whose germs have originated as ectodermal inclusions in the early embryo; while such growths as originate at a later period, from the spongioblast in the embryo, or from the developed ependymal cell of the ventricles or the chorioid plexuses in the adult, must be regarded as gliomata.

Herein may perhaps lie an explanation of the infrequency with which carcinoma occurs in the brain, and the relatively greater frequency of glioma.

And, indeed, in the absence of evidence to the contrary, there is no good reason to believe that those neoplasms, already described in the literature as cerebral carcinoma, may not have been glioma of organoid type —that is, tumors which have the same ultimate histogenesis as carcinoma, but which correspond with the cell of a later developmental stage. Such a tumor would complete the scheme of classification for glioma suggested by Dr. Flexner, in which certain well-known types are referred to certain forms or stages of development of neuroglia. And as there are types whose cells correspond with the astroblast, others whose cells are

like the astrocytes, and still others composed of the embryonic ependymal cell, so the tumor in question would correspond with the fully developed or adult ependymal cell. Such an organoid tumor would perhaps represent a type between carcinoma and the simple glioma.

What then is the probable nature of the tumor described? This question is not easy to answer, and different observers would doubtless be led to conclusions somewhat contrary. There would seem, however, to be more than a possibility that the tumor, primary in the cerebral substance, sprang from adult ependymal epithelium which was included within the depth of the cerebral substance, and that the growth was entirely separated from the ventricles at the time of the autopsy.

As to the relation of the tuberculosis to the neoplasm, the former everywhere pervades the tumor as diffuse tubercle tissue or as discrete microscopical nodules. The tubercle tissue is more marked in certain areas than in others, and is most developed in the stroma and the capsule. Tubercle bacilli and typical giant cells are present.

The acute inflammatory exudate must likewise be regarded as a tuberculous product, since no other causative agent could be found.

The tumor is often broken up by the diffuse infiltration of tubercle cells and polymorphonuclear leucocytes. The tuberculosis must therefore be regarded as secondary to the tumor formation both because of the diffuse infiltrating character of the tubercle tissue and because of its limited extent.

The primary focus of the tuberculous infection is more difficult to determine. The tuberculous lesion of the brain itself was demonstrated only upon microscopical examination, so it can not be said that the primary focus did not exist elsewhere in the body. But in the absence of such evidence the brain tumor must be regarded as a *locus minoris resistentiæ* which favored the development of tubercle.

There is but little literature upon this subject.

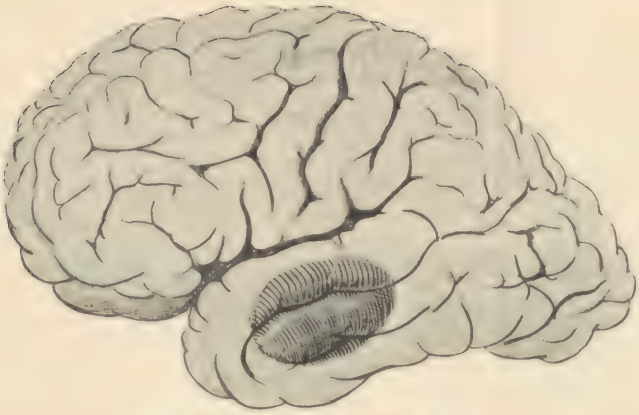

FIG. 1.—Diagram of brain with tumor *in situ*.

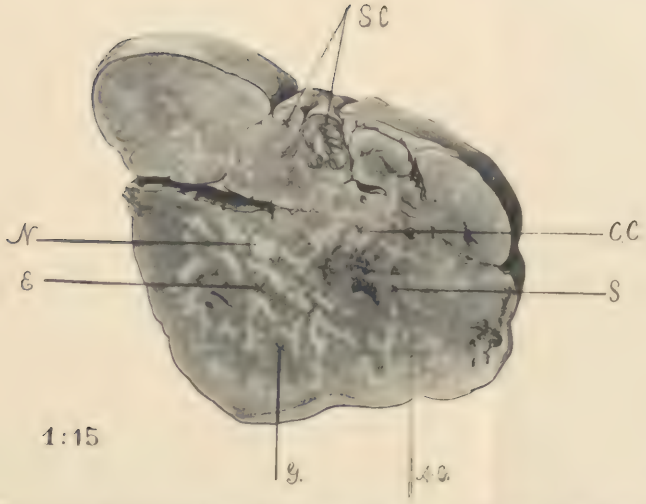

FIG. 2.—Cross section of tumor after alcohol hardening. Enlarged four times. *S C*, area resembling simple carcinoma; *C C*, area resembling carcinoma with large branching alveoli; *S*, area resembling simple sarcoma; *A G*, and *G*, areas resembling glioma; *E*, area resembling endothelioma; *N*, area of necrosis.

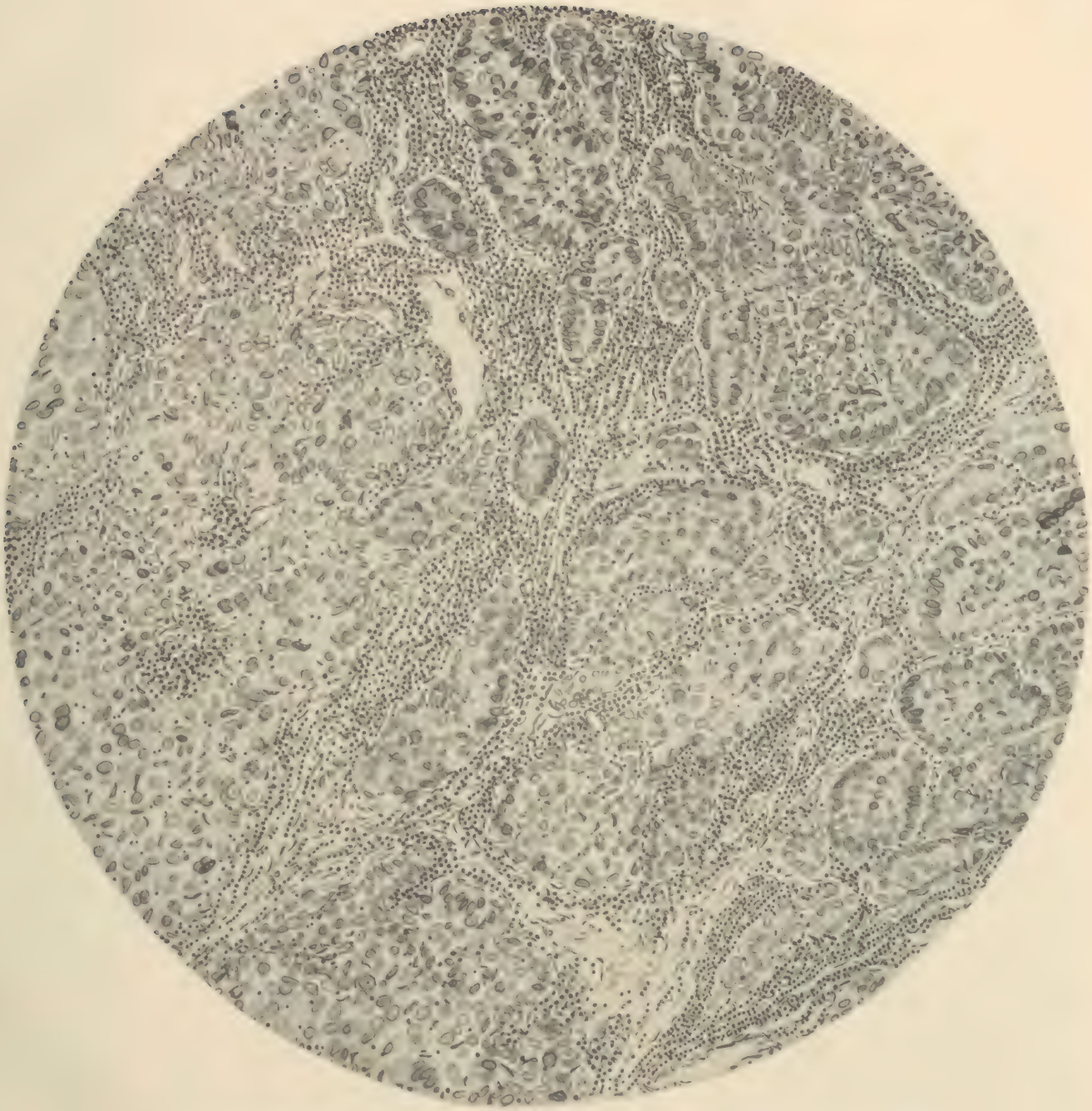

Fig. 8.—Area resembling simple medullary carcinoma. Hæmatoxylin and eosin stain. Zeiss objective A A, ocular No. 8.

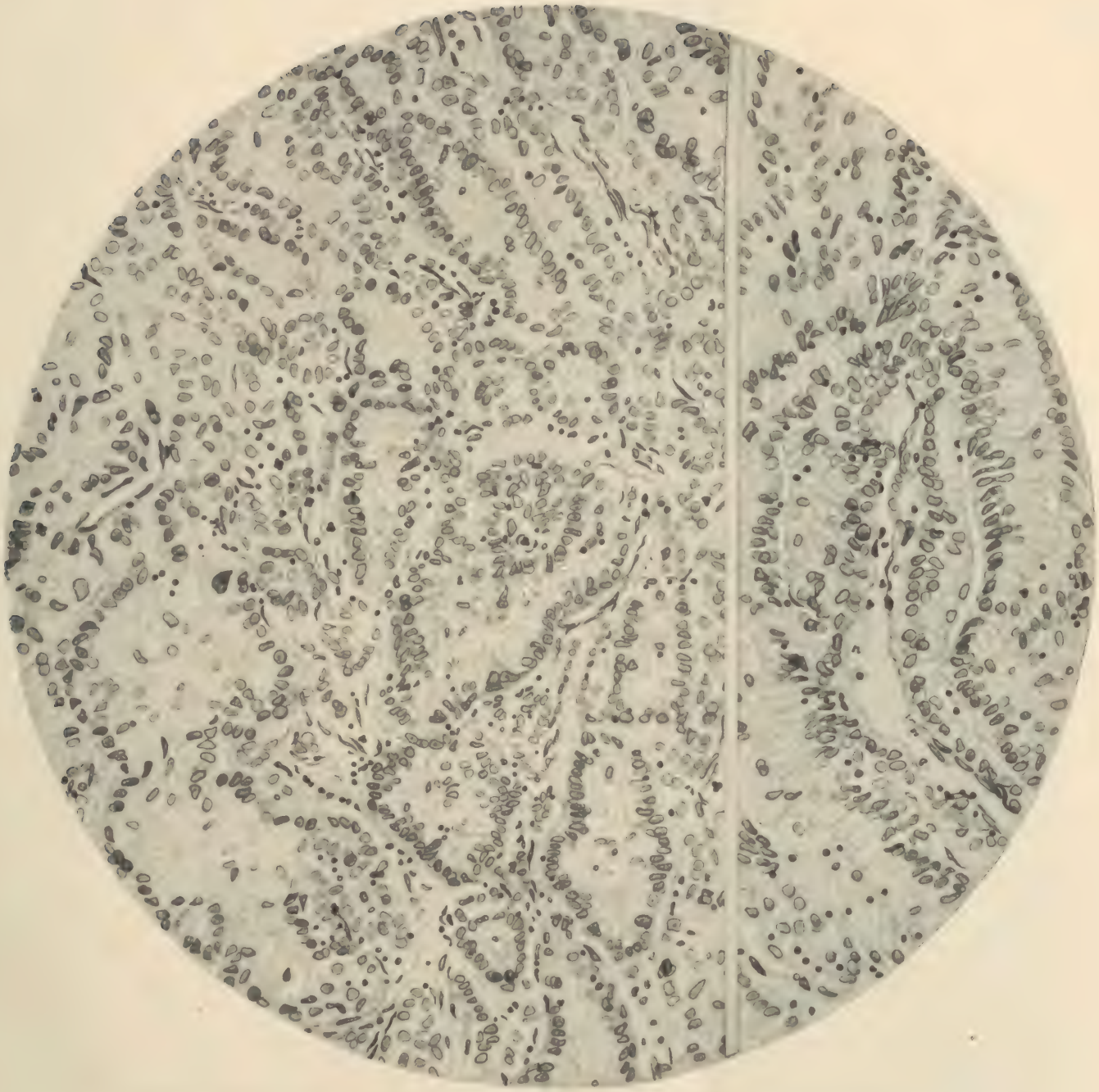

FIG. 4.—*a*, Area resembling tubular carcinoma ; *b*, blood-vessel surrounded by a double row of cylindrical cells. Hæmatoxylin and eosin stain. Zeiss objective A A, ocular No. 5.

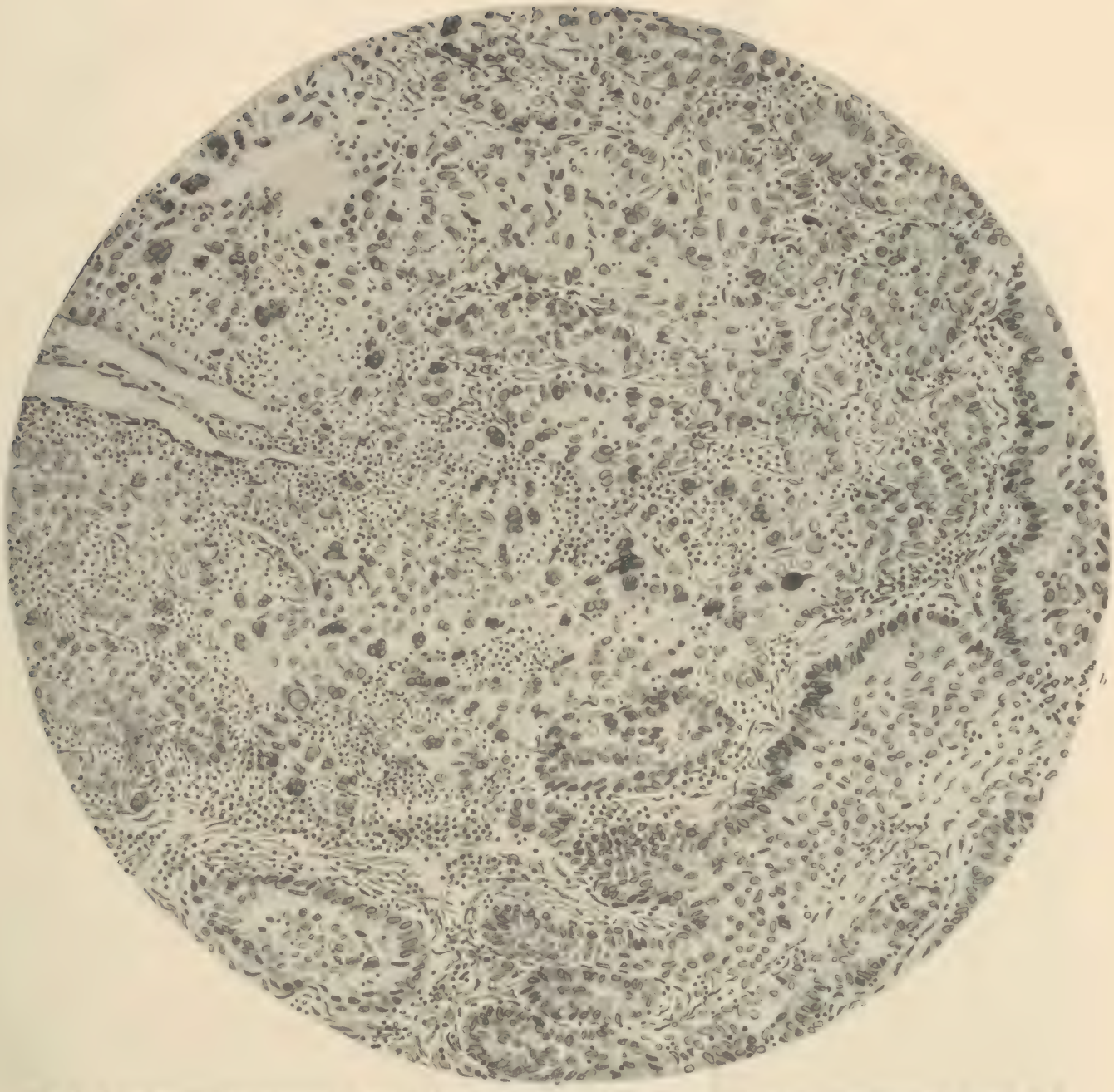

Fig. 5.— *a*, Area resembling simple sarcoma ; *b*, margin of large branching alveolus. Hæmatoxylin and eosin stain. Zeiss objective A A, ocular No. 5.

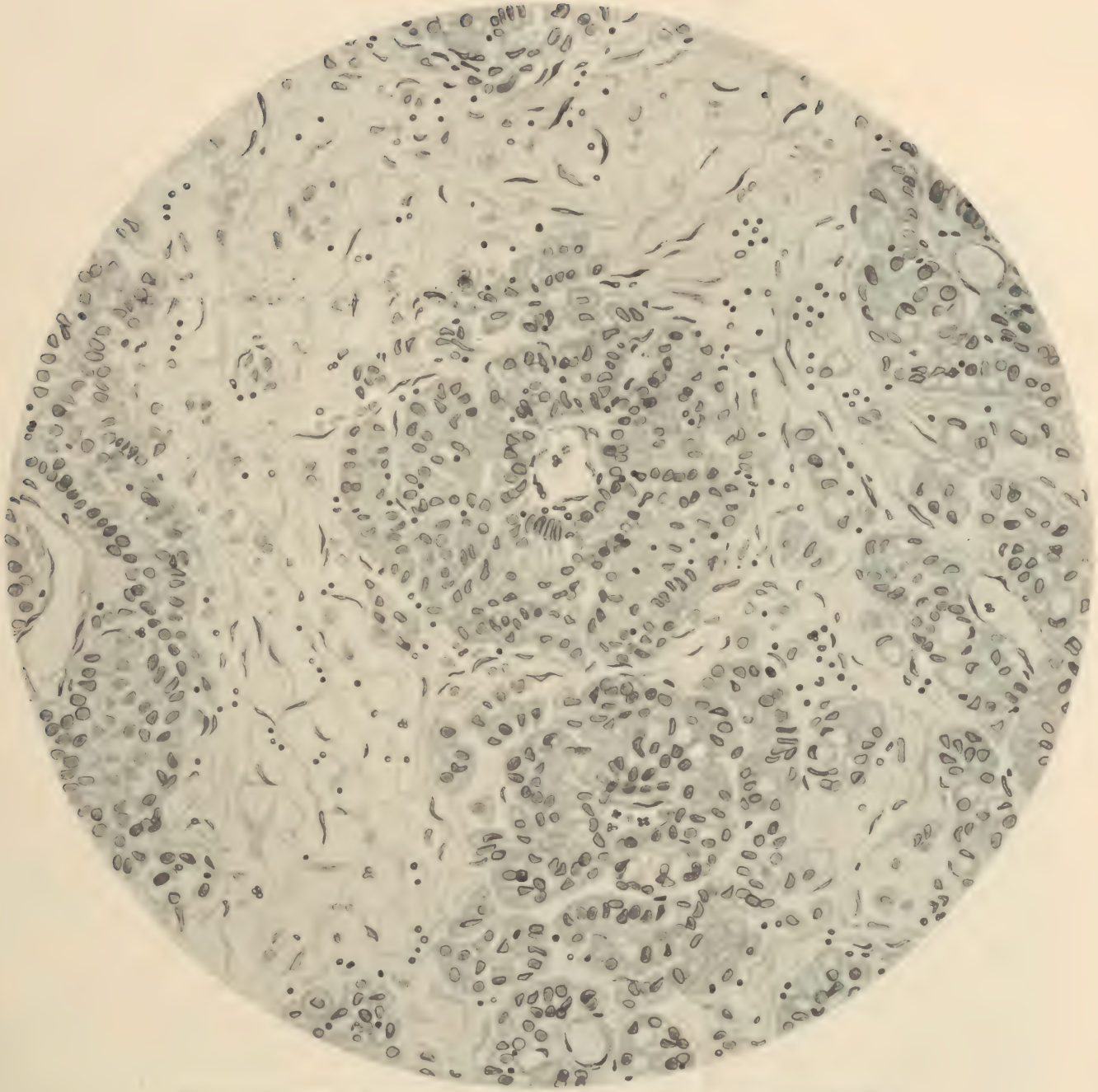

FIG. 6.—Area resembling endothelioma. Hæmatoxylin and eosin stain. Zeiss objective A A, ocular No. 5.

One case has been brought to my notice in which tuberculosis complicated a case of glioma. Perhaps in the future it will be shown for brain tumors, as has already been shown for neoplasms elsewhere in the body, that this association is not so uncommon.

In conclusion, I wish to thank Dr. Flexner for many valuable suggestions during the course of this work, and Mr. Brödel and Mr. Becker for kind criticism of the drawings.

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